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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,323	YOSHIDA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,8 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6, 8, and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 4/23/03. Claims 4, 5, 6, 8, 10, and 12-15 have been amended, claims 7 and 9 have been cancelled, and claim 16 has been added. Claims 4-6, 8, and 10-16 are pending. Applicant's amendments and arguments have been thoroughly reviewed. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Drawings

2. The drawings filed 4/23/03 are approved. The drawings submitted as Figures 4, 5, 6, and 8 are not acceptable for examination because the drawings are illegible. New drawings are required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because it is not clear how the electrophoresis gel itself can carry out the method step listed in the claim. That is, it is not clear if the "further comprising" recited in claim 13 is meant to mean the gel further comprises the labeling or that the method further

comprises the recited step. Amendment of claim 13 to recite, "according to claim 12, wherein the method further comprises" would overcome the rejection.

Prior Art Rejections

5. The claims are drawn to DNA data containing mediums that are obtained by means of a recited method of analysis. Thus, the claims are product by process type claims. It is noted that product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps (see MPEP 2113).

Claim Rejections - 35 USC § 103

6. Claims 4, 5, 6, 8, 9, 12, 13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatada *et al.* (PNAS USA, 88, p. 9523-9527) in view of both Carrano *et al.* (Genomics 4, 129-136 (1989)) and the New England Biolabs Catalog. .

This rejection applies to claims 4, 5, 6, 12, 13, and 15 and 16 when they are interpreted such that the DNA data containing medium is a gel which contain DNA fragments that were treated as recited in the claims.

Hatada *et al.* teach a genomic DNA analytical pattern which has been obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme (MluI) which is capable of cutting the genomic DNA so that the 3' end of the recognition site has a protruding sticky end

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme and subjecting the resultant restricted fragments to electrophoresis to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme and subjecting the resultant restricted, fractionated fragments to electrophoresis to bring about a second-dimensional fractionation

Hatada *et al.* teach that one advantage of their method is that the scanning field of the method can be extended by the use of different kinds of landmarks (the first restriction enzyme) and further suggest the use of rare cutting enzymes (p. 9525, Col. 2). Hatada *et al.* provide examples of such enzymes, such as BssHII, an enzyme with a six nucleotide recognition site.

Hatada *et al.* provide photographs of the electrophoresis gels that are produced by their methods in Figures 2-4.

Hatada *et al.* do not teach a method for making a DNA data containing medium in which in which the labeling of step (b) is accomplished by ligating a labeled adapter to the restriction site.

Carrano et al. teach a method for labeling restriction fragments which comprises the addition of a fluorescently labeled adaptor to the end of the restriction fragment (p. 130). Carrano et al. teach "because fluorescence instead of radioactivity is measured, fragment size resolution is improved and more information may be obtained...(p. 130)" and they further teach that "the method is sufficiently universal that it can be applied to other DNA analysis schemes...(p. 136)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Hatada *et al.* by labeling the restriction fragments with labeled adaptors instead of filling in the overhangs. The ordinary practitioner would have been motivated to modify the methods of Hatada et al. in order to take advantage of

the benefits of using the fluorescent adaptors taught by Carrano et al. Furthermore, with regard to claim 5, it would have been prima facie obvious to have added more than one labeled base to the adaptor, because additional labels would have increased signal intensity.

Hatada et al. in view of Carrano *et al.* do not teach genomic DNA containing mediums which were created via use of a first restriction enzyme that includes at least one "N" wherein N recognizes any of A, G, C, or T. However, Hatada et al. do teach that the method can be extended to the use of any other rare cutting enzymes. Furthermore, Carrano et al. teach that custom primers can be synthesized for ligating labeled adaptors to "most other" restriction ends (p. 136).

New England Biolabs provides a number of different restriction enzymes, including many rare cutters that have "N" in the recognition sequence (for example BstXI, Bg1I, and MwoI). In particular, the enzyme BglI taught in the catalog has NNNN in the recognition site, and the N's in the recognition site can include any of A, G, C, or T. Furthermore, New England Biolabs provides information as to whether or not the restriction enzymes are methylation sensitive.

It would have been prima facie obvious to have modified the teachings of Hatada et al. in view of Carino et al. by utilizing any of the rare cutting enzymes provided by New England Biolabs. The ordinary practitioner would have been motivated to use alternative rare cutting enzymes by the teachings provided by Hatada et al. (who suggest extending the methods to other landmark enzymes), Carino et al. (who teach that "most other" restriction ends can be ligated to), and by New England Biolabs who provide a variety of restriction enzymes for sale via their catalog in order to provide additional methods for the study of genomic DNA.

7. Claims 4, 5, 6, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki *et al.* (Electrophoresis, 1993, 14, 251-258) in view of Carrano *et al.* (Genomics 4, 129-136 (1989)).

Hayashizaki *et al.* teach a genomic DNA analytical pattern which has been obtained by means of a method of analysis comprising:

(a) treating genomic DNA with a first restriction enzyme that is sensitive to methylation of the genomic DNA (NotI or BssHII) which is capable of cutting the genomic DNA so that the 3' end of the recognition site has a protruding sticky end

(b) labeling the cleavage site

(c) treating the resulting DNA fragments with a second restriction enzyme to bring about first-dimensional fractionation

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme to bring about second-dimensional fractionation; and

(e) detecting the spots of the labeled DNA fragments fractionated in step (d) (Hayashizaki *et al.* describes method p. 256-257).

Hayashizaki *et al.* provide photographs of the electrophoresis gels that are produced by their methods in Figure 7.

Hayashizaki *et al.* do not teach a method for making a DNA data containing medium in which in which the labeling of step (b) is accomplished by ligating a labeled adapter to the restriction site.

Carrano et al. teach a method for labeling restriction fragments which comprises the addition of a fluorescently labeled adaptor to the end of the restriction fragment (p. 130).

Carrano et al. teach "because fluorescence instead of radioactivity is measured, fragment size resolution is improved and more information may be obtained...(p. 130)" and they further teach that "the method is sufficiently universal that it can be applied to other DNA analysis schemes...(p. 136)."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Hayashizaki *et al.* by labeling the restriction fragments with labeled adaptors instead of filling in the overhangs. The ordinary practitioner would have been motivated to modify the methods of Hayashizaki et al. in order to take advantage of the benefits of using the fluorescent adaptors taught by Carrano et al.

With regard to the limitation of claim 10 that the recognition sequence of the restriction enzyme includes Ns, where each N can be an of A, G, C, or T, this limitation essentially includes any possible restriction enzyme, because each recognizes a sequence that contains either an A, G, C, or T, so therefore any restriction enzyme recognizes "N" as defined by the claim. This is further highlighted by the dependent claim that recites that the first restriction can be one of NotI, AccIII, or BssHII, two of which are specifically used by Hayashizaki *et al.* Thus, the rejection is maintained over this newly added limitation of claim 10.

Response to Remarks

All of the previous rejections under 112 2nd paragraph are withdrawn in light of the amendments to the claims, with the exception of the rejection of claim 13, which was not overcome by amendment to the claim.

The rejections for anticipation under 102 were overcome by amendment of the claims to further define the subject matter of the claimed invention.

The 103 rejections are modified to address the amendments to the claims, but are largely maintained as in the previous action, and thus applicant's arguments against the 103 rejections are addressed. Applicant argues that the instant method is distinctly different from the method taught by Hatada *et al.* because the method of Hatada *et al.* involves labeling both ends of the fragments as opposed to selectively labeling with adapters. This is not persuasive. The methods of the instant invention are drawn using "comprising" language and do not appear to be limited as applicants arguments suggest.

Furthermore, the rejection must be considered as a whole. Hatada *et al.* teach a method wherein either the 5' end or the 3' end of a sample is labeled depending on which restriction enzyme was used, and different labeling methods were used for each case (p. 9523). Applicant appears to be arguing that when one combines the methods of Hatada *et al.* with Carrano *et al.* that all fragments will not be labeled as a result. This is not persuasive, because it is not clear how applicant would come to this conclusion. Carrano *et al.* exemplify methods of labeling 5' protruding ends with adapters and further teach that an analogous method could be applied to "blunt ends and 3' overhangs (p. 136)," and thus there is no reason why the combination of the two methods would not have resulted in labeling as many of the cut fragments as Hatada *et al.* labeled. The difference is only in the method of labeling, and Carrano *et al.* specifically motivate using adapters instead of direct labeling with radioactive nucleotides when they state "because fluorescence instead of radioactivity is measured, fragment size resolution is improved

and more information may be obtained...(p. 130)" and they further teach that "the method is sufficiently universal that it can be applied to other DNA analysis schemes...(p. 136)."

Applicant argues that because Carrano *et al.* exemplifies adding adapters to a 3' overhang the person of ordinary skill in the art would not have been able to produce the presently claimed invention. However, this is not persuasive, as Carrano *et al.* specifically teach that their method could just as easily be applied to 3' overhangs (p. 136).

Finally, applicant argues that there is no motivation to modify Hatada *et al.* to use Carrano *et al.* since the RLGS method does not espouse using adapters but directly labeling the cleavage site. Again, specific motivation is provided in the rejection from the teachings of Carrano *et al.* to utilize their labeling method as opposed to a radioactive based method such as the one used by Hatada *et al.* Applicant argues that the use of adapters in the method of Hatada et al would necessarily impede the very objective of the RGLS method, but provides no evidence for this assertion. As noted previously, there is no reason why the labeling method used by Carrano *et al.* would not be as effective as that used by Hatada *et al.* If applicant is implying that the method would be less efficient, it is noted that this is a results optimizable variable and that the one of ordinary skill in the art would have known to use enough adapter to effect efficient ligation and labeling.

No separate arguments are set forth against the rejection in voew of Hayashizaki *et al.* in view of Carrano *et al.*

Conclusion

8. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

July 9, 2003

GARY BENZION, PH.D
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